REMARKS

1. Status of the Claims

Claims 26, 27, 30, 32-35, 37, 38, and 41-45 are pending.

Claims 26, 37-40 have been amended in order to clarify the relative basis for the amount of the ingredients in the composition and process of the present invention.

In claim 26, support for the amount of ritonavir can be found in the Specification on page 11 lines 25-28, page 14 lines 29-32, and examples 1-16 (20% of ritonavir), 17-20 (30% of ritonavir) and 21-24 (10% of ritonavir). Support for the step (a) can be found at page 16 lines 30-32 until page 17 lines 1-4 and 23-28 of the specification as filed. Support for the amount of the alcoholic co-solvent can be found at page 12 lines 9-12 and examples 1-24 (compositions comprising 10% of propylene glycol) of the Specification as filed. Support for the amount of medium chain mono/diglycerides mixture can be found at page 12 lines 28-31 and examples 5, 6, 11-13, 19, 20 and 23 of the specification as filed; support for the amount of antioxidant can be found at page 13 lines 18-20 and examples 1, 2, 5, 7, 9, 11, 13-16 (0.025% of BHT), examples 3, 4, 6, 8, 10, 12 (0.050% of BHT), examples 17-20 (0.075% of BHT) and examples 21-24 (0.0125% of BHT) of the specification as filed. Support for the amount of emulsion-stabilizing agent can be found at page 14 lines 1-3 and examples 5, 6, 11-16, 19, 20, 22-24 (compositions comprising PEG 400) of the specification as filed. Support for the amount of polarity corrector can be found at page 14 lines 10-12 and examples 7-12 and 24 (compositions comprising citric acid) and examples 13 and 14 (compositions comprising ascorbic acid) of the specification as filed.

In claim 37, support for the amount of the alcoholic solvent can be found at page 12 lines 5-8 and examples 1-24 (composition comprising 12% of ethanol) of the specification as filed. Support for the amount of the alcoholic co-solvent can be found at page 12 lines 9-12 and examples 1-24 (compositions comprising 10% of propylene glycol) of the specification as filed. Support for the amount of medium chain mono/diglycerides mixture can be found at page 12 lines 28-31 and examples 5, 6, 11-13, 19, 20 and 23 of the specification as filed. Support for the amount of the surfactant can be found at page 13 lines 1-11 and examples 1-4, 7-10, 15-19 and 21-24 (6% of polyethoxylated castor oil 35), examples 5, 6, 11, 12 and 20 (10% of polyethoxylated castor oil 35) and examples 13 and

14 (5% of polyethoxylated castor oil 35) of the specification as filed. Support for the amount of antioxidant can be found at page 13 lines 18-20 and examples 1, 2, 5, 7, 9, 11, 13-16 (0.025% of BHT), examples 3, 4, 6, 8, 10, 12 (0.050% of BHT), examples 17-20 (0.075% of BHT) and examples 21-24 (0.0125% of BHT) of the specification as filed.

No new matter has been added.

2. Interview Summary

Applicants thank the Examiner and her Supervisor for speaking with their representatives on May 19, 2009. During the Interview, the indefiniteness rejection, the written description rejection, and the obviousness rejection were discussed. Applicants pointed to data in the Pacheco Declaration filed with the Amendment of June 3, 2008 (Pacheco Declaration 1, particularly [0013] and [0014]) which was relevant to both the Bailey Reference and the Lipari Reference, as discussed further below. No agreement was reached, but Applicants' representatives sincerely thank the Examiner for taking the time and effort to speak with them.

3. Declaration

Applicants herein provide a second Declaration from Dr. Pacheco (Pacheco Declaration 2) addressing each of the Examiner's concerns regarding the amounts of the ingredients in the present invention (Pacheco Declaration 2, page 16, particularly paragraphs [0021]-[0022]), the significance of the steps in the process of making the present invention (Pacheco Declaration 2, page 6, Experiment 2), and a comparison of the present invention to the Lipari reference (Pacheco Declaration 2, page 10-11). The citations recited here will be further discussed below.

4. Claim rejections under 35 USC §112, second paragraph

The Examiner rejects claims 26-27, 30-35 as indefinite. The Examiner states that there is a general disclosure of the steps and examples of the final composition but not of the starting amounts or ranges.

The legal test for indefiniteness is whether those skilled in the art would understand what is claimed when the claim is read in light of the Specification. *Seattle Box Co. v. Industrial Crating & Packing Inc.*, 221 USPQ 568, 574 (Fed.Cir. 1984); *In re Morasi*, 218 USPQ 289, 292 (Fed.Cir. 1983). Applicants respectfully submit that the claims would be clear to one of skilled art for the reasons discussed below.

i. Percent Weight/Weight of Final Composition

Applicants submit that the amount of each ingredient in the inventive process and product resulting therefrom is clear. The claims recite the amount of each starting material in %w/w that means *the percentage of each material in relation to the final weight of the composition.* (Specification, page 12, lines 8 and 28-30). Such representation (%w/w) is a common practice in the pharmaceutical field and one of average skill in the art certainly would be capable of defining such amounts according to the present Specification. Applicants have also amended the claims to further clarify the amount of each ingredient. Accordingly, Applicants submit that one of skill would have understood what is claimed based on the claims. Applicants request that the rejection be withdrawn.

ii. Starting Weight and Amount of Alcohol

The Examiner also states that the starting weight is unclear and that the quantity of alcohol used to correct the final weight is not described. Applicants respectfully disagree.

As shown in Pacheco Declaration 2 the amount of ritonavir which is initially added in the inventive process is does not significantly differ from the final amount. Specifically, Dr. Pacheco discloses a loss of approximately 0.3% of ritonavir. (Pacheco Declaration 2, page 16, Experiment 4, particularly [0021]). As ritonavir is **not** added at *any other* time during the claimed process, (claim 26, Pacheco Declaration [0022]), one of skill would know *exactly* how much ritonavir would be needed to achieve a desired amount and would find

the presently claimed method "clearly described by the claims." (*Id.*). Accordingly, Applicants request that the rejection be withdrawn.

Also, the Specification presents working examples which describe the amount of ingredients used in accordance with the present invention. (Specification, page 23-35). Each example discloses a composition prepared in accordance with the invention's method in a batch amount, (Specification, page 36, lines 23-24), and filled into soft gelatin capsules in a quantity of 500mg/capsule or 1000mg/capsule. So, 500mg or 1000mg can be used as the final weight of the composition (100%) in order to find the amount of each ingredient of the composition/capsule since the percentages in weight of the ingredients in relation to the final weight of the composition are given in the examples. The result will be the quantity/capsule. If one wishes to produce 1000 capsules of 500mg, the final weight of the composition would be 500g.

For instance, the composition of the example 6, when filled into soft gelatin capsules in a quantity of 500mg/capsule, confers a ritonavir dose of 100mg/capsule. The table below summarizes the quantity of the each ingredient per capsule.

Ingredient	**% w/w**	**Quantity/capsule mg**	**Quantity/capsule mg**
Ritonavir	20.00	100	200
Ethanol	12.00	60	120
Propylene glycol	10.00	50	100
Medium chain mono/diglycerides (AKOLINE MCM)	23.475	117.375	234.75
Polyethylene glycol 400(Peg 400)	23.475	117.375	234.75
Butylated hydroxy toluene (BHT)	0.050	0,25	0,50
Polyethoxylated castor oil 35	10.00	50	100
Water	1.000	5	10
Total	100	500	1000

The examples show that the desired final amounts of the composition ingredients are the same of those added during the manufacturing process with the exception of the ethanol (which is evaporated after the dissolution and filtration steps to the desired amount in the final composition). However, as discussed below, the amount of ethanol needed at each step would be clear to one of skill in the art.

iii. The Amount of Ethanol in Step (a) of the process

In claim 26, step (a) requires dissolving an amount of ritonavir in an amount of ethanol; step (c) requires evaporating the ethanol to concentrate the amount of ritonavir, (e) distilling the composition to adjust for a specific amount of alcoholic solvent, and step (g) requires correcting the final percent of ritonavir in the final composition by adding an amount of ethanol, if necessary.

The Examiner indicates that the amount of ethanol used is unclear. The initial amount of ethanol is greater than its final amount in the composition. Due to this practical condition, the process requires adjusting the desired amount of ethanol in the steps (c), (e) and (g) to obtain the desired concentrations in the final composition.

As the amount of the ingredients, with exception of ethanol, does not vary substantially during the process for preparation of pharmaceutical compositions of ritonavir, it is clear to a person skilled in the art that an eventual difference in the desired final weight of the composition is due only to the change in the amount of ethanol. The Specification as filed discloses the entire procedure for the preparation of the claimed concentrated pharmaceutical composition at page 17, line 23 to page 18, line 20, and page 22, lines 15-32.

A person skilled in the art is able to understand from the Specification that the process for preparation of 500g of the composition of the example 6 of the instant application, which is enough to prepare 1000 capsules of 500mg/capsule, involves the steps of:

(a) dissolving ritonavir (100g; 20% w/w) in sufficient amount of an alcohol solvent of C_2-C_4 (ethanol; at least 2 x 60g in view of the disclosure of step (c)) to obtain a clear solution, at a temperature between 30°C and 45°C to make a first mixture;

(b) eliminating particles from said first mixture by filtration;

(c) evaporating the alcoholic solvent from the filtered first mixture under reduced pressure at a temperature not higher than 40°C to about half of its initial volume;

(d) adding to the filtered and concentrated first mixture an alcoholic co-solvent (propylene glycol; 50 g; 10% w/w), a medium chain mono/diglycerides mixture (AKOLINE MCM; 117.375g; 23.475% w/w), an antioxidant in an amount

ranging from 0.001% to 2% w/w of the final composition, an emulsion-stabilizing agent (Polyethylene glycol 400; 117.375g; 23.475% w/w) and a polarity corrector (not added for the composition of example 6) to make a second mixture;

(e) removing the alcoholic solvent of step (a) from said second mixture by distilling under reduced pressure to correct the weight of said second mixture until the remaining quantity of alcoholic solvent (ethanol) is 60g (12% w/w);

(f) adding to the distilled second mixture a surfactant (polyethoxylated castor oil 35; 50g; 10% w/w) under continuous stirring, until the second mixture becomes a clear solution, thereby obtaining a stable and concentrated ritonavir pharmaceutical composition; and

(g) correcting, if necessary, the final weight of the pharmaceutical composition (500g) by adding the alcoholic solvent (ethanol) employed in the step (a) to obtain a solution comprising 100g (20% w/w) of ritonavir.

If the process is not carried following the steps described in claim 26, it is not possible to obtain the final composition in form of a stable solution of ritonavir. This fact was clearly demonstrated in the declaration by Pacheco Declaration 1 and filed with the Amendment filed June 3, 2008. (See Pacheco Declaration 1, [0005] and [0058]). Accordingly, Applicants submit that one of skill would recognize how much ethanol is applied in each step.

iv. *Indefiniteness conclusion*

Because one of skill would understand what percent weight of the composition means, would understand the insignificant effect of the filtering step, and would recognize how much ethanol is needed at the beginning and end of the process for making the composition, Applicants respectfully request that the rejection based on lack of definiteness be withdrawn.

5. Claim rejections under 35 USC §112 – Written Description

The Examiner rejects claims 26-27, 30, and 32-35 as not supported by sufficient written description. Applicants respectfully disagree.

As explained above, Applicants have shown that the Specification as filed clearly describes the amounts of the ingredients used in each step of the claimed process for preparation of a pharmaceutical composition of ritonavir. The Specification indicates that the filtration step is important to remove solid particles which could trigger precipitation, page 17, lines 28-31. From this, one of skill would recognize that the amount of ritonavir is consistent from the beginning of the process to the end of the process. Moreover, Applicants have confirmed for the Examiner's benefit that, as one of skill in the art would recognize, the filtration step does not remove a significant amount of ritonavir quantitatively, but that the step is qualitatively important. (Pacheco Declaration, page 16, Experiment 4). Thus, Applicants submit that the presently claimed invention is amply supported by the disclosure in the Specification as filed.

Accordingly, Applicant respectfully requests that the rejection based on lack of adequate written description be withdrawn.

6. Claims rejection under 35 USC §103

Applicants first address the rejection of the process claims and then address the rejection of the product claims, as the product claims require every limitation of the process claims.

(a). Lipari in view of Bailey and CU Boulder Organic Chemistry Undergraduate Courses, Lab Techniques.

The Examiner rejects claims 26, 27, 30, and 32-35 as unpatentable over Lipari in view of Bailey as applied to claims 37-45 and further in view of CU Boulder Organic Chemistry Undergraduate Courses, Lab Techniques. This rejection is respectfully traversed. Reconsideration and withdrawal thereof are requested.

i. The combination of Lipari, Bailey, and CU Boulder does not disclose each step of the claimed process.

Claims 26 etc. are directed to a process for preparing a ritonavir composition. As discussed below, Applicants submit that the Examiner has failed to establish that the combination of Lipari and Bailey discloses the recited amounts of each ingredient of the claimed invention.

Furthermore, and perhaps more persuasive of patentability, the combination of Lipari, Bailey and CU Boulder *does not describe the process of the claimed invention.* Specifically, Bailey teaches heating of the monoglycerides, antioxidant, and PVP to 55-60°C and then addition to, mixing, and dissolution of the previously "sieved" proteinase inhibitor in the monoglycerides/antioxidant/PVP solution. (See Bailey, Example 1). Lipari teaches mixing alcohol and oleic acid while "warmed" between 28-37°C, warmed "as necessary", or at 23-33°C, and then adding the antioxidant, castor oil, and ritonavir. (*See e.g.*, Lipari, Examples 7, 9, 10, 29). **Neither reference teaches dissolving ritonavir in ethanol** (claim 26, step (a)). CU Boulder does not remedy this deficiency. Thus, the Examiner has failed to make a *prima facie* case of obviousness of the **claimed invention**.

ii. The presently claimed process generates a product showing unexpected stability.

Moreover, Applicants submit that the presently claimed process presents unexpected results which overcome any showing of *prima facie* obviousness that the Examiner may have established. The Specification discloses that the solution resulting from the claimed process does not have "microcrystalline forms or solid particles that are capable of triggering the crystallization of the less soluble polymorph" of ritonavir.[1] (Specification, page 18, line 29-30). The Specification indicates that the stability and clarity of the solution are a direct result of the claimed process.

This conclusion is supported in both Pacheco Declarations 1 and 2. Pacheco Declarations 1 and 2 show unequivocally that using a process in which ritonavir is added directly to the other ingredients ("direct addition") does not result in a clear solution. Please see the following table:

[1] Applicants recognize that the Examiner was concerned about the identity of the various polymorphs based on the disclosure of the Specification. Applicants submit that the polymorphs discussed in the Specification correlate to the general understanding in the art, that is polymorph II (the less soluble polymorph in the Specification) is the polymorph form II recognized in the art to be less soluble than form I. The Examiner has provided no evidence that one of skill would not understand this correlation based on the disclosure in the Specification, therefore, Applicants address this concern only in passing.

	Ingredients of the present invention	**Ingredients of Bailey with ritonavir**	**Ingredients of present invention with oleic acid of Lipari**
Method of the Present Invention	**Clear, stable solution-** (Specification, Pacheco Declaration 2, Experiment 3(i) and 3(ii) page 12, figure 5)		**Not stable-** becomes cloudy in 48 hours at room temperature (Pacheco Declaration, Experiment 3(ii), pages 12-13, Figure 5)
Direct Addition	**Opaque solution-** (Pacheco Declaration 2, Experiment 1(ii), pages 7-9, Figure 3; Pacheco Declaration 1, page 9, paragraphs [0032] and [0034], Figures 7 and 8)	**Solution is solid-** (Pacheco Declaration 2, Experiment 1, pages 4-5, Figure 1; Pacheco Declaration 1, Experiments a, b, a1 and b1)	**Opaque, ritonavir not dissolved-** (Pacheco Declaration 2, Experiment 3(iii) pages14-15, Figure 6)

Only by using the ingredients of the present invention and the process recited in the claims is a clear, stable solution obtained.

The Examiner includes CU Boulder Organic Chemistry Undergraduate Courses, Lab Techniques solely for its disclosure of a conventional technique of vacuum distillation. Nothing in this additional reference remedies the failure of the combination of Lipari with Bailey to establish *prima facie* obviousness of the present invention or to discredit the showing of the Pacheco Declarations. Accordingly, the instant rejection fails. Applicants request that the instant rejection be withdrawn.

(b). Lipari et al (US Patent 6,232,333) in view of Bailey et al (US Patent 6,008,228)

The Examiner rejects claims 37-45 under 35 USC § 103(a) as being unpatentable over Lipari in view of Bailey. Claims 37-45 are product-by-process claims. This rejection is respectfully traversed. Reconsideration and withdrawal thereof are requested.

i. Pacheco Declaration 2 demonstrates that the claimed inventive products are not obvious.

The Examiner indicates that the product that would result from the combination of Lipari and Bailey would have been obvious.

Applicants submit that both the ingredients of the composition and the process by which the composition is made establishes that the present invention is not obvious.

ii. *The Examiner fails to make a* prima facie *case of obviousness because the amount of glycerides is not the result of routine optimization.*

First, the Examiner fails to establish *prima facie* obviousness of the invention. The Examiner asserts that the range of the amount of glycerides in the composition represents merely routine optimization. However, the range of glycerides mixture is not a result of routine experimentation.

Rather, considering the references *as a whole*, the wide range taught by the references suggests that the glyceride ingredient is not a result-effective variable. The Examiner should consider that, even if finding an optimal range of an ingredient in a composition might be obvious generally, discovering that a particular ingredient is the one that must be manipulated to obtain that result can be non-obvious. *See, e.g. In re Antonie*, 195 USPQ 6 (CCPA 1977). Second, an artisan of ordinary skill, attempting to determine optimum and operable conditions would not have arrived at the range 20-40% mono-di-glycerides because Bailey teaches that the amount of monoglycerides alone is at least 40%, and the amount of the combined glycerides would be a significantly higher percentage of the total composition. Thus, one of skill would not have any expectation of success in achieving the presently claimed stable solution of ritonavir by substituting the oleic acid of Lipari with the mono/diglyceride solution of Bailey.

	Monoglyceride Content of the mono/diglyceride solution	**Diglyceride Content of the mono/diglyceride solution**	**Total amount of monoglycerides in the final composition**
INWITTOR	50%	40%	40-80% (Bailey's reference)
CAPMUL MCM or CAPMUL MCM 90	70% (but generally 83-95%)	30% (generally 5-17%	40-80% (Bailey's reference)
AKOLINE	50-32%	38-40%	10-12.4% monoglycerides when AKOLINE is 20% of final composition (as disclosed in the present application)
AKOLINE	50-62%	38-40%	20-24.8% monoglycerides when ALKONINE is 40% of the final composition (as the limit specified in claim 10 of the present application)

Thus, the prior art cited fails to disclose or suggest at least one element of the presently claimed invention and the instant rejection fails.

Even further, Pacheco Declaration 2 conclusively establishes that the oleic acid of Lipari is not equivalent to the mono/diglyceride mixture of Bailey. (Pacheco Declaration 2, Experiment 3, page 10-13). Specifically, when oleic acid (as described in Lipari) is used with the other ingredients of the claimed invention, *in the claimed process,* it results in a solution which is not stable after 48 hours at room temperature.

Accordingly, Applicants request that the Examiner withdraw the obviousness rejection.

iii. Unexpected Results: The claimed process generates an unexpectedly stable product.

Applicants submit that the presently claimed ritonavir product is not obvious because the claimed process provides the product with unexpected stability. Under the MPEP, once the Examiner has provided a rationale which allegedly shows that that the claimed product appears to be the same or similar to that of the prior art, the Applicant may come forward with evidence establishing an unobvious difference between the claimed product and the prior art product. MPEP § 2113.

As shown by Pacheco Declarations, using the ingredients of the present invention by a direct addition method as disclosed in Bailey and Lipari does not result in the claimed product, that is, a stable solution of ritonavir. (Pacheco Declaration 2, Experiment 1(ii), pages 7-9, Figure 3; Pacheco Declaration 1, page 9, paragraphs [0032] and [0034], Figures 7 and 8).

Applicants submit that this evidence showing the significance of the claimed process steps overcomes any *prima facie* case of obviousness that the Examiner may have established regarding the claimed product and so have met their burden of proof. Applicants therefore request that the rejection be withdrawn.

iv. The Examiner improperly dismissed Pacheco Declaration 1.

As an aside, the Examiner has improperly failed to consider that evidence (Pacheco Declaration 1). The Examiner asserts that the product with the closest composition is Lipari, not Bailey and in a product comparison, the comparison would be to Lipari product, thus considering the Pacheco Declaration (submitted with the Amendment dated June 3, 2008) as not relevant to the rejection. Applicants respectfully disagree.

First and foremost, the legal requirement for a comparative experiment for a showing to rebut an assertion of *prima facie* obviousness is that the embodiment of the invention closest to the prior art of record be compared with that embodiment. See, e.g. *In re Merchant*, 197 USPQ 785 (CCPA 1978). Whatever the feelings of the Examiner on the issue of what constitutes the closest prior art, Dr. Pacheco quite clearly explains that it is the composition of Bailey that is the closest prior art between the two cited references. See, paragraph [005] on page 2 of the Pacheco Declaration. The Examiner is cautioned that she must not substitute her judgment for that of a Declarant. See, e.g. *In re Katschmann,* 146 USPQ 66 (CCPA 1965).

However, to further prosecution, Applicants have provided a second Declaration from Dr. Pacheco. Applicants maintain, however, that the Examiner's statement of the "closest prior art" is incorrect.

In any case, Applicants submit that both Declarations definitively state that the artisan of ordinary skill in the art reading the cited references in fact would not have an expectation of success in making the present invention. That is, the result obtained by the present invention is unexpected by the artisan of ordinary skill who reads Lipari and Bailey.

Applicants have demonstrated by evidence on the record that the present invention provides an unexpected result over the prior art of record, and therefore the instant rejection should be withdrawn for this additional reason.

CONCLUSION

Applicants submit that the present claims clearly describe subject matter well-described in the Specification that is novel and inventive over the prior art of record. The favorable actions of withdrawal of the standing rejections and allowance of the present claims are requested.

If the Examiner has any questions or comments, please contact the undersigned by telephone to discuss the matter.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17, particularly, extension of time fees.

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Respectfully submitted,

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Attachments: Pacheco Declaration 2